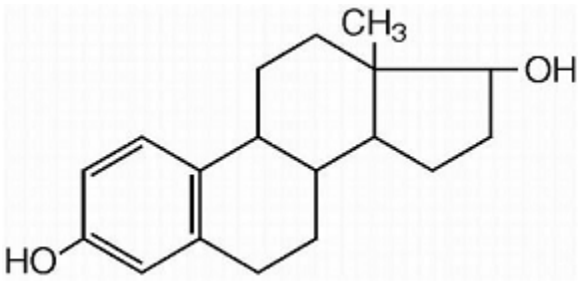
ESTRACE - estradiol cream
Warner Chilcott (US), LLC

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses. (See WARNINGS, Malignant neoplasms, *Endometrial cancer*.)
CARDIOVASCULAR AND OTHER RISKS
Estrogens with or without progestins should not be used for the prevention of cardiovascular disease. (See WARNINGS, Cardiovascular disorders.)
The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. (See CLINICAL PHARMACOLOGY, Clinical Studies.)
The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens-plus-medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen-alone therapy. (See CLINICAL PHARMACOLOGY, Clinical Studies.)
Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

Each gram of ESTRACE® (estradiol vaginal cream, USP, 0.01%) contains 0.1 mg estradiol in a nonliquefying base containing purified water, propylene glycol, stearyl alcohol, white ceresin wax, mono- and di-glycerides, hypromellose 2208 (4000 cps), sodium lauryl sulfate, methylparaben, edetate di-sodium and *tertiary*-butylhydroquinone. Estradiol is chemically described as estra-1,3,5(10)-triene-3,17β-diol. It has an empirical formula of $C_{18}H_{24}O_2$ and molecular weight of 272.37. The structural formula is:



CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.
Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.
Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

Pharmacokinetics

Absorption

Estrogen drug products are absorbed through the skin, mucous membranes, and the gastrointestinal tract after release from the drug formulation.

Distribution
The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism
Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion
Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Special Populations
No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

Drug Interactions
In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Clinical Studies

Women's Health Initiative Studies
The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of oral 0.625 mg conjugated estrogens (CE) per day alone or the use of oral 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The CE/MPA substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index". Results of the CE/MPA substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 1 below:

Table 1. RELATIVE AND ABSOLUTE RISK SEEN IN THE CE/MPA SUBSTUDY OF WHI[*]

Event[†]	Relative Risk CE/MPA vs placebo at 5.2 Years (95% CI[‡])	Placebo n = 8102	CE/MPA n = 8506
		Absolute Risk per 10,000 Women-years	
CHD events	1.29 (1.02 - 1.63)	30	37
Non-fatal MI	*1.32 (1.02 - 1.72)*	*23*	*30*
CHD death	*1.18 (0.70 - 1.97)*	*6*	*7*
Invasive breast cancer[§]	1.26 (1.00 - 1.59)	30	38
Stroke	1.41 (1.07 - 1.85)	21	29
Pulmonary embolism	2.13 (1.39 - 3.25)	8	16
Colorectal cancer	0.63 (0.43 - 0.92)	16	10

Endometrial cancer	0.83 (0.47 - 1.47)	6	5
Hip fracture	0.66 (0.45 - 0.98)	15	10
Death due to causes other than the events above	0.92 (0.74 - 1.14)	40	37
Global Index †	1.15 (1.03 - 1.28)	151	170
Deep vein thrombosis ¶	2.07 (1.49 - 2.87)	13	26
Vertebral fractures ¶	0.66 (0.44 - 0.98)	15	9
Other osteoporotic fractures ¶	0.77 (0.69 - 0.86)	170	131

*****adapted from JAMA, 2002; 288:321-333
†a subset of the events was combined in a “global index”, defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes
‡nominal confidence intervals unadjusted for multiple looks and multiple comparisons
§includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer
¶not included in Global Index

For those outcomes included in the "global index”, the absolute excess risks per 10,000 women-years in the group treated with CE/MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the “global index” was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNINGS, WARNINGS,** and **PRECAUTIONS**.)

Women’s Health Initiative Memory Study
The Women’s Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of CE/MPA (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the estrogen/progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS** and **WARNINGS**, **Dementia.**)

INDICATIONS AND USAGE
ESTRACE (estradiol vaginal cream, USP, 0.01%) is indicated in the treatment of vulvar and vaginal atrophy.

CONTRAINDICATIONS
ESTRACE (estradiol vaginal cream, USP, 0.01%) should not be used in women with any of the following conditions:
1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of cancer of the breast.
3. Known or suspected estrogen-dependent neoplasia.
4. Active deep vein thrombosis, pulmonary embolism or history of these conditions.
5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6. Liver dysfunction or disease.
7. ESTRACE (estradiol vaginal cream, USP, 0.01%) should not be used in patients with known hypersensitivity to its ingredients.
8. Known or suspected pregnancy. There is no indication for ESTRACE (estradiol vaginal cream, USP, 0.01%) in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See **PRECAUTIONS**.)

WARNINGS
See **BOXED WARNINGS**.

Systemic absorption may occur with the use of ESTRACE (estradiol vaginal cream, USP, 0.01%). The warnings, precautions, and adverse reactions associated with oral estrogen treatment should be taken into account.

1. Cardiovascular disorders

Estrogen and estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

a. ***Coronary heart disease and stroke***

In the Women's Health Initiative (WHI) study, an increase in the number of myocardial infarctions and strokes has been observed in women receiving CE compared to placebo. These observations are preliminary, and the study is continuing. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In the CE/MPA substudy of WHI, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs 30 per 10,000 women-years). The increase in risk was observed in year one and persisted.

In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA (0.625 mg/2.5 mg per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. ***Venous thromboembolism (VTE)***

In the Women's Health Initiative (WHI) study, an increase in VTE has been observed in women receiving CE compared to placebo. These observations are preliminary, and the study is continuing. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the CE/MPA group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant neoplasms

a. ***Endometrial cancer***

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile

than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. ***Breast cancer***

The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) substudy of CE/MPA (see **CLINICAL PHARMACOLOGY**, **Clinical Studies**). The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration.

The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about five years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen-alone therapy.

In the CE/MPA substudy, 26% of the women reported prior use of estrogen-alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01 - 1.54), and the overall absolute risk was 41 vs 33 cases per 10,000 women-years for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs 25 cases per 10,000 women-years for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen-plus-progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

3. Dementia

In the Women's Health Initiative Memory Study (WHIMS), 4,532 generally healthy postmenopausal women 65 years of age and older were studied, of whom 35% were 70 to 74 years of age and 18% were 75 or older. After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n = 2,229) and 21 women in the placebo group (0.9%, n = 2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% confidence interval 1.21 – 3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies** and **PRECAUTIONS, Geriatric Use.**)

It is unknown whether these findings apply to estrogen-alone therapy.

4. Gallbladder disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

5. Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

6. Visual abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

PRECAUTIONS

A. GENERAL

1. ***Addition of a progestin when a woman has not had a hysterectomy***
Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer.

2. ***Elevated blood pressure***
In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

3. ***Hypertriglyceridemia***
In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

4. ***Impaired liver function and past history of cholestatic jaundice***
Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

5. ***Hypothyroidism***
Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. ***Fluid retention***
Because estrogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

7. ***Hypocalcemia***
Estrogens should be used with caution in individuals with severe hypocalcemia.

8. ***Ovarian cancer***
The CE/MPA substudy of WHI reported that estrogen-plus-progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% confidence interval 0.77 – 3.24) but was not statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen alone, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

9. ***Exacerbation of endometriosis***
Endometriosis may be exacerbated with administration of estrogens. A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

10. ***Exacerbation of other conditions***
Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

B. PATIENT INFORMATION
Physicians are advised to discuss the PATIENT INFORMATION leaflet with patients for whom they prescribe ESTRACE (estradiol vaginal cream, USP, 0.01%).

C. LABORATORY TESTS

Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (e.g., estradiol, FSH).

D. DRUG/LABORATORY TEST INTERACTIONS

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. Patients on thyroid replacement therapy may require higher doses of thyroid hormone. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered.

3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL_2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

7. Reduced serum folate concentration.

E. CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS**.)

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

F. PREGNANCY

ESTRACE (estradiol vaginal cream, USP, 0.01%) should not be used during pregnancy. (See **CONTRAINDICATIONS**.)

G. NURSING MOTHERS

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when ESTRACE (estradiol vaginal cream, USP, 0.01%) is administered to a nursing woman.

H. PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established. Large and repeated doses of estrogen over an extended period of time have been shown to accelerate epiphyseal closure, resulting in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. In patients in whom bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended.

Estrogen treatment of prepubertal children also induces premature breast development and vaginal cornification, and may potentially induce vaginal bleeding in girls. In boys, estrogen treatment may modify the normal pubertal process. All other physiological and adverse reactions shown to be associated with estrogen treatment of adults could potentially occur in the pediatric population, including thromboembolic disorders and growth stimulation of certain tumors. Therefore, estrogens should only be administered to pediatric patients when clearly indicated and the lowest effective dose should always be utilized.

I. GERIATRIC USE

In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of 4 years, 82% (n = 3,729) were 65 to 74 while 18% (n = 803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens-plus-medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated

estrogens-plus-medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of women that were older than 70. (See **WARNINGS, Dementia.**)
There have not been sufficient numbers of geriatric patients involved in studies utilizing ESTRACE (estradiol vaginal cream, USP, 0.01%) to determine whether those over 65 years of age differ from younger subjects in their response to ESTRACE (estradiol vaginal cream, USP, 0.01%).

ADVERSE REACTIONS

See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS**.
Systemic absorption may occur with the use of ESTRACE (estradiol vaginal cream, USP, 0.01%). The warnings, precautions, and adverse reactions associated with oral estrogen treatment should be taken into account.
The following additional adverse reactions have been reported with estrogen and/or progestin therapy.

1. Genitourinary system

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea, increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; application site reactions of vulvovaginal discomfort including burning and irritation; genital pruritus; ovarian cancer; endometrial hyperplasia; endometrial cancer.

2. Breasts

Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.

3. Cardiovascular

Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

4. Gastrointestinal

Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis, enlargement of hepatic hemangiomas.

5. Skin

Chloasma or melasma, that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.

6. Eyes

Retinal vascular thrombosis, intolerance to contact lenses.

7. Central nervous system

Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy, dementia.

8. Miscellaneous

Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthralgias; leg cramps; changes in libido; urticaria, angioedema, hypersensitivity, anaphylactoid/anaplylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing drug products by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

Use of ESTRACE (estradiol vaginal cream, USP, 0.01%), alone or in combination with a progestin, should be limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should reevaluate periodically as clinically appropriate (e.g., 3-month to 6-month intervals) to determine if treatment is still necessary (see **BOXED WARNINGS** and **WARNINGS**). For treatment of vulvar and vaginal atrophy associated with the menopause, the lowest dose and regimen that will control symptoms should be chosen and medication should be discontinued as promptly as possible. For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.
Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals.
Usual Dosage: The usual dosage range is 2 to 4 g (marked on the applicator) daily for one or two weeks, then gradually reduced to one half initial dosage for a similar period. A maintenance dosage of 1 g, one to three times a week, may be used after restoration of the vaginal mucosa has been achieved.

NOTE: The number of doses per tube will vary with dosage requirements and patient handling.

HOW SUPPLIED

ESTRACE® (estradiol vaginal cream, USP, 0.01%).
N 0430-3754-14: Tube containing 1 ½ oz (42.5 g) with a calibrated plastic applicator for delivery of 1, 2, 3, or 4 g.
Store at room temperature. Protect from temperatures in excess of 40° C (104° F).
Keep ESTRACE Vaginal Cream out of the reach of children.

INFORMATION FOR THE PATIENT
(Updated September 2009)
NOTE: The number of doses per tube will vary with dosage requirements and patient handling.

Read this PATIENT INFORMATION before you start using ESTRACE® Vaginal Cream and read what you get each time you refill ESTRACE Vaginal Cream. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT ESTRACE VAGINAL CREAM (AN ESTROGEN HORMONE)?

- **Estrogens increase the chances of getting cancer of the uterus.**

Report any unusual vaginal bleeding right away while you are taking estrogens. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

- **Do not use estrogens with or without progestins to prevent heart disease, heart attacks, or strokes.**

Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. Using estrogens with progestins may increase your risk of dementia. You and your healthcare provider should talk regularly about whether you still need treatment with ESTRACE Vaginal Cream.

What is ESTRACE Vaginal Cream?

ESTRACE Vaginal Cream is a medicine that contains estrogen hormones.
What is ESTRACE Vaginal Cream used for?

ESTRACE Vaginal Cream is used to:

- treat moderate to severe dryness, itching, and burning in and around the vagina due to menopause. You and your healthcare provider should talk regularly about whether you still need treatment with ESTRACE Vaginal Cream to control these problems.

Who should not use ESTRACE Vaginal Cream?

Do not start using ESTRACE Vaginal Cream if you:

- **have unusual vaginal bleeding**
- **currently have or have had certain cancers**

Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should use ESTRACE Vaginal Cream.

- **had a stroke or heart attack in the past year**
- **currently have or have had blood clots**
- **currently have or have had liver problems**
- **are allergic to ESTRACE Vaginal Cream or any of its ingredients**

See the end of this leaflet for a list of ingredients in ESTRACE Vaginal Cream

• **think you may be pregnant**

Tell your healthcare provider:

• **if you are breastfeeding**

The hormone in ESTRACE Vaginal Cream can pass into your milk.

• **about all of your medical problems**

Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

• **about all the medicines you take**

This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how ESTRACE Vaginal Cream works. ESTRACE Vaginal Cream may also affect how your other medicines work.

• **if you are going to have surgery or will be on bed rest.**

You may need to stop taking estrogens.

How should I use ESTRACE Vaginal Cream?

1. Remove cap from tube. (There is no seal on tube)
2. Do not separate plunger from applicator.
3. Screw threaded end of applicator onto the opened tube until secure.
4. Position upright in order to view the calibrated gram amounts.
5. Gently squeeze tube from the bottom to expel the prescribed amount of ESTRACE Vaginal Cream into the applicator. As cream is squeezed out, plunger will rise to indicate amount of grams.
6. Unscrew applicator from tube.
7. Replace cap onto tube.
8. Lie on back with knees drawn up. To deliver medication, gently insert applicator deeply into the vagina and press plunger downward to its original position.
9. To cleanse applicator: Pull plunger to remove it from barrel. Wash with mild soap and warm water. DO NOT BOIL OR USE HOT WATER.

ESTRACE Vaginal Cream should be used at the lowest dose possible for your treatment only as long as needed. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with ESTRACE Vaginal Cream.

What are the possible side effects of ESTRACE Vaginal Cream?

Although ESTRACE Vaginal Cream is only used in and around the vagina, the risks associated with oral estrogens should be taken into account.
Less common but serious side effects include:

• Breast cancer

• Cancer of the uterus

• Stroke

- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.
Common side effects include:

- Headache
- Breast tenderness
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss
- Vaginal burning, irritation, and itching

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus (“fibroids”)
- Vaginal yeast infection
- Allergic Reactions

These are not all the possible side effects of ESTRACE Vaginal Cream. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of a serious side effect with ESTRACE Vaginal Cream?

Talk with your healthcare provider regularly about whether you should continue using ESTRACE Vaginal Cream. See your healthcare provider right away if you get vaginal bleeding while using ESTRACE Vaginal Cream. Have a breast exam and mammogram (breast x-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often. If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease.

General information about safe and effective use of ESTRACE Vaginal Cream

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use ESTRACE Vaginal Cream for conditions for which it was not prescribed. Do not give ESTRACE Vaginal Cream to other people, even if they have the same symptoms you have. It may harm them.

Keep ESTRACE Vaginal Cream out of the reach of children.

This leaflet provides a summary of the most important information about ESTRACE Vaginal Cream. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about ESTRACE Vaginal Cream that is written for health professionals. You can get more information by calling the toll free number 1-800-521-8813.

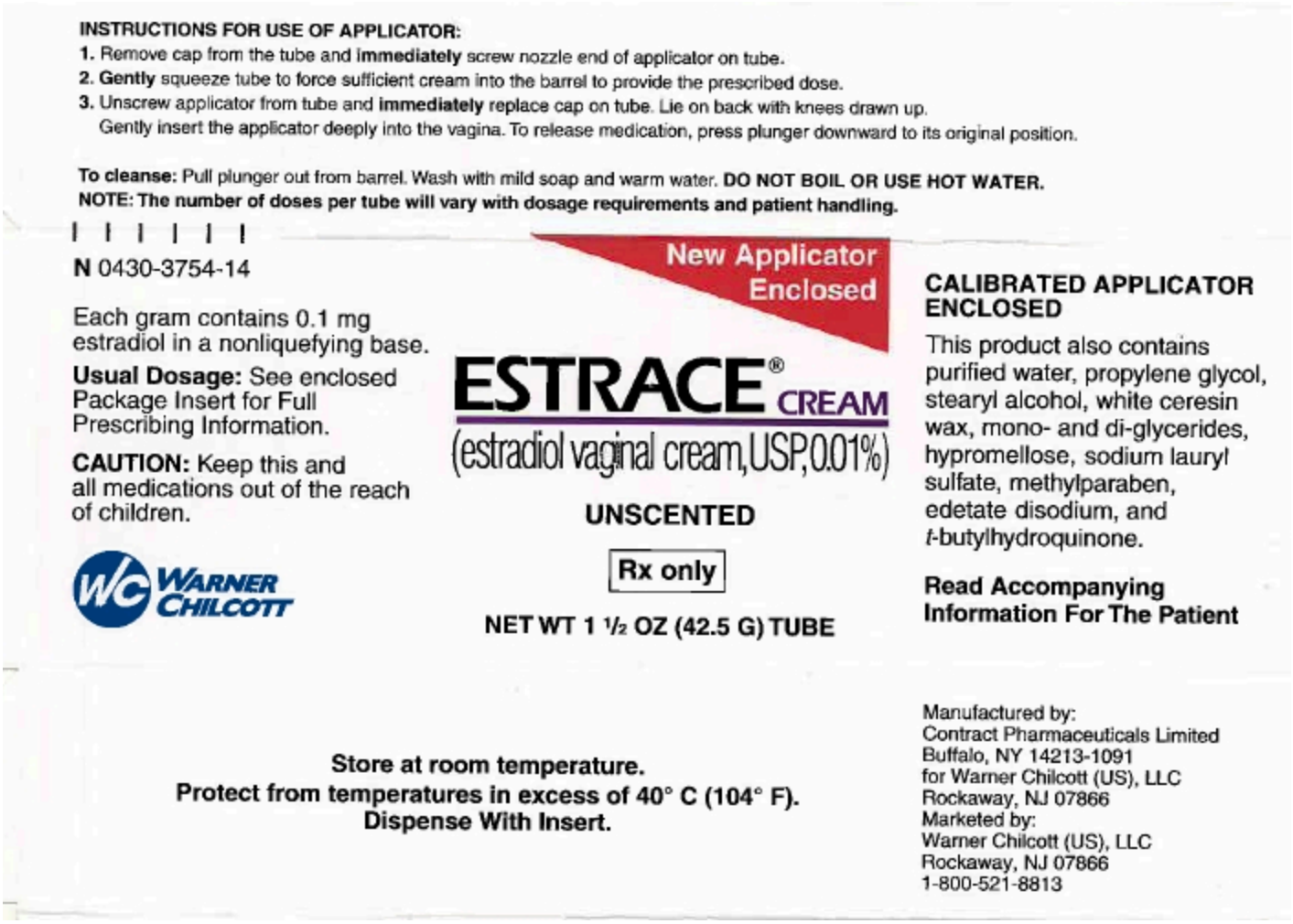
What are the ingredients in ESTRACE Vaginal Cream?

Each gram of ESTRACE Vaginal Cream contains 0.1 mg estradiol in a nonliquefying base containing purified water, propylene glycol, stearyl alcohol, white ceresin wax, mono- and di-glycerides, hypromellose 2208 (4000 cps), sodium lauryl sulfate, methylparaben, edetate di-sodium and *tertiary*-butylhydroquinone.

Manufactured by:
Contract Pharmaceuticals Limited
Buffalo, NY 14213-1091
for Warner Chilcott (US), LLC
Rockaway, NJ 07866
Marketed by:
Warner Chilcott (US), LLC
Rockaway, NJ 07866
1-800-521-8813
To report SUSPECTED ADVERSE REACTIONS, contact Warner Chilcott at 1-800-521-8813 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

3754G059 Revised: September 2009

PRINCIPAL DISPLAY PANEL - CARTON LABEL - 1½ OZ (42.5 G)



INSTRUCTIONS FOR USE OF APPLICATOR:
1. Remove cap from the tube and **immediately** screw nozzle end of applicator on tube.
2. **Gently** squeeze tube to force sufficient cream into the barrel to provide prescribed dose.
3. Unscrew applicator from tube and **immediately** replace
cap on tube. Lie on back with knees drawn up. Gently insert the applicator deeply into the vagina. To release medication, press plunger downwa
To cleanse: Pull plunger out from barrel. Wash with mild soap and warm water. **DO NOT BOIL OR USE HOT WATER.**
NOTE: The number of doses per tube will vary with dosage requirements and patient handling.
N 0430-3754-14
Each gram contains 0.1 mg estradiol in a nonliquefying base.
Usual Dosage: See enclosed Package Insert for Full Prescribing Information.
CAUTION: Keep this and all medication out of the reach of children.
ESTRACE® CREAM (estradiol vaginal cream, USP, 0.01%)
UNSCENTED
Rx only
NET WT 1½ OZ (42.5 G) TUBE
Store at room temperature.
Protect from temperatures in excess of 40° C (104° F).
Dispense With Insert.
CALIBRATED APPLICATOR ENCLOSED
This product also contains purified water, propylene glycol, stearyl alcohol, white ceresin wax, mono- and di-glycerides, hypromellose, sodium lauryl sulfate, methylparaben, edetate disodium and *t*-butylhydroquinone
Read Accompanying Information For The Patient

Revised: 09/2009 Distributed by: Warner Chilcott (US), LLC